such as paclitaxel can be added to a combination of MDM2 inhibitor ("MDM2i") and trametinib, which can lead to further synergistic effect or strong induction of apoptosis. A combination of the MDM2 inhibitor with a Bcl2 inibitor can be supplemented by a BRAF inhibitor (e.g. dabrafenib) and CMET inhibitor (e.g. PF-04217903) to form a quadruple combination. The latter combination was found to be weakly synergistic, but with strongly inducing apoptosis.

[0017] In another aspect, the present disclosure relates to a pharmaceutical composition comprising the pharmaceutical combination of the disclosure and at least one pharmaceutically acceptable carrier.

[0018] In one aspect, the present disclosure relates to the pharmaceutical combination or the pharmaceutical composition of the disclosure for use as a medicine.

[0019] In another aspect, the present disclosure relates to the pharmaceutical combination or the pharmaceutical composition of the disclosure for use in the treatment of cancer.

[0020] In another aspect, the disclosure provides the use of to the pharmaceutical combination of the disclosure for the preparation of a medicament for the treatment of a cancer.

[0021] In yet another aspect, the present disclosure relates to a method for treating cancer in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a pharmaceutical combination of the present disclosure, or the pharmaceutical composition of the present disclosure.

[0022] Specifically, the present disclosure provides the following aspects, advantageous features and specific embodiments, respectively alone or in combination, as listed in the claims below.

BRIEF DESCRIPTION OF THE DRAWINGS

[0023] FIG. **1** Dose-response curves for 8 TP53 wild-type colorectal cancer cell lines for the MDM2 inhibitor (S)-1-(4-Chloro-phenyl)-7-isopropoxy-6-methoxy-2-(4-{methyl-[4-(4-methyl-3-oxo-piperazin-1-yl)-trans-cyclohexylmethyl]-amino}-phenyl)-1,4-dihydro-2H-isoquinolin-3-one (COMPOUND A) (circle) and the MEK inhibitor trametinib (triangle) and their combination (diamond). The x-axis indicates the log10 of the treatment dilution; the y-axis indicates the cell count after treatment relative to DMSO. Combinations result from a fixed-ratio (1:1) combination of the single agents. The strong dashed line indicated the number of cells before the start of the treatment ('baseline').

[0024] FIG. **2** Dose-response curves for 8 TP53 wild-type colorectal cancer cell lines for the MDM2 inhibitor (6S)-5-(5-Chloro-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-6-(4-chlorophenyl)-2-(2,4-dimethoxypyrimidin-5-yl)-1-(propan-2-yl)-5,6-dihydropyrrolo[3,4-d]imidazol-4(1H)-one (COMPOUND B) (circle) and the MEK inhibitor trametinib (triangle) and their combination (diamond). The x-axis indicates the log10 of the treatment dilution; the y-axis indicates the cell count after treatment relative to DMSO. Combinations result from a fixed-ratio (1:1) combination of the single agents. The strong dashed line indicated the number of cells before the start of the treatment ('baseline').

[0025] FIG. **3** Isobologram analysis at the 75% inhibition level for combinations of the MDM2 inhibitor (S)-1-(4-Chloro-phenyl)-7-isopropoxy-6-methoxy-2-(4-{methyl-[4-(4-methyl-3-oxo-piperazin-1-yl)-trans-cyclohexylmethyl]-amino}-phenyl)-1,4-dihydro-2H-isoquinolin-3-one (COMPOUND A) or the MDM2 inhibitor (6S)-5-(5-Chloro-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-6-(4-chlorophenyl)-2-(2,4-dimethoxypyrimidin-5-yl)-1-(propan-2-yl)-5,6-dihydropyrrolo[3,4-d]imidazol-4(1H)-one (COMPOUND B) (y-axis) with the MEK inhibitor trametinib (x-axis) over 8 TP53 wild-type colorectal cancer cell lines. Points on the diagonal curve indicate an additive effect, points to the right of it an antagonism, and points to the left of it synergy. The hollow circle shows the combination with the lowest combinations index (strongest synergy) (see Table 2 for the value).

[0026] FIG. **4** Maximum Caspase 3/7 induction for the MDM2 inhibitor (S)-1-(4-Chloro-phenyl)-7-isopropoxy-6-methoxy-2-(4-{methyl-[4-(4-methyl-3-oxo-piperazin-1-yl)-trans-cyclohexylmethyl]-amino}-phenyl)-1,4-dihydro-2H-isoquinolin-3-one (COMPOUND A), the MEK inhibitor trametinib and their combination in 5 TP53 wild-type colorectal cancer cell lines and after 24 h, 48 h, and 72 h (different shades of grey). The x-axis indicates the treatment; the y-axis indicates the maximum Caspase 3/7 induction (% of cells) seen for each treatment.

[0027] FIG. **5** Long-term colony formation assays for single agents and combination of the MDM2 inhibitor (S)-1-(4-Chloro-phenyl)-7-isopropoxy-6-methoxy-2-(4-{methyl-[4-(4-methyl-3-oxo-piperazin-1-yl)-trans-cyclohexylmethyl]-amino}-phenyl)-1,4-dihydro-2H-isoquinolin-3-one (COMPOUND A) and the MEK inhibitor trametinib. "COMPOUND A (L)": 0.33□M; "COMPOUND A (H)": 1□M; "trametinib (L)" for all but LIM2405 and SW48: 4 nM; "trametinib (H)" for all but LIM2405 and SW48: 12 nM; "trametinib (L)" for LIM2405 and SW48: 1 nM, "trametinib (H)" for LIM2405 and SW48: 3 nM. (A) Representative images of cells after crystal violet staining. (B) Quantification of crystal violet signal from (A). Bars show average±standard deviation for n=3 replicates. For significance test see Table 3. RFU=relative fluorescence unit.

[0028] FIG. **6** FACS analysis for the MDM2 inhibitor (S)-1-(4-Chloro-phenyl)-7-isopropoxy-6-methoxy-2-(4-{methyl-[4-(4-methyl-3-oxo-piperazin-1-yl)-trans-cyclohexylmethyl]-amino}-phenyl)-1,4-dihydro-2H-isoquinolin-3-one (COMPOUND A), the MEK inhibitor trametinib and their combination after 24 h treatment. "COMPOUND A (L)": 0.33□M; "COMPOUND A (H)": 1□M; "trametinib (L)" for all but LIM2405 and SW48: 4 nM; "trametinib (H)" for all but LIM2405 and SW48: 12 nM; "trametinib (L)" for LIM2405 and SW48: 1 nM, "trametinib (H)" for LIM2405 and SW48: 3 nM. The stacked bars indicate the percentage of the cell population in each of the cell cycle phases: subG1, G1, S, and G2.

[0029] FIG. **7** Western blot analysis of the MDM2 inhibitor (S)-1-(4-Chloro-phenyl)-7-isopropoxy-6-methoxy-2-(4-{methyl-[4-(4-methyl-3-oxo-piperazin-1-yl)-trans-cyclohexylmethyl]-amino}-phenyl)-1,4-dihydro-2H-isoquinolin-3-one (COMPOUND A), the MEK inhibitor trametinib and their combination after 24 h treatment. "COMPOUND A (L)": 0.33□M; "COMPOUND A (H)": 1□M; "trametinib (L)" for all but LIM2405 and SW48: 4 nM; "trametinib (H)" for all but LIM2405 and SW48: 12 nM; "trametinib (L)" for LIM2405 and SW48: 1 nM, "trametinib (H)" for LIM2405 and SW48: 3 nM.

[0030] FIG. **8** qRT-PCR analysis of 5 target genes for of the MDM2 inhibitor (S)-1-(4-Chloro-phenyl)-7-isopropoxy-6-methoxy-2-(4-{methyl-[4-(4-methyl-3-oxo-piperazin-1-yl)-trans-cyclohexylmethyl]-amino}-phenyl)-1,4-dihydro-2H-isoquinolin-3-one (COMPOUND A), the MEK inhibitor trametinib and their combination after 10 h treatment.